

Aktuelles Management der cystischen Fibrose (CF)

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Management bei CF

- Vermeidung gesundheitlicher Beeinträchtigungen
 - In körperlicher
 - In psychischer
 - In sozialer Hinsicht
- **Ziel:**
 - Gesundheitserhaltung (jetzt und zukünftig) - „holistischer Ansatz“

Zielgruppen für Management

1. „gesund“: Säugling, Kleinkind
durch Screening entdeckt
2. „übliche“ CF Patient (prä-1997)
3. „burnt-out“ Patienten
end-stage lung, respiratory failure, Prä-TX
4. Erwachsenen-Probleme
Fertilität, CFDM, Depressionen, Osteoporose,
Schmerzen, Inkontinenz
5. Pat. mit Komplikationen (DIOS, Pneu, ABPA)
6. Der „atypische“ CF Patient („CF-related“)

CF-Management

- **Grundlagen**
 - Zentrumsmedizin
 - CF = Multiorganerkrankung
- **Gesichertes - Etabliertes**
 - Ernährung, Antibiotika, Physiotherapie
- **Neues - in der Diskussion**
 - Entzündungshemmer
 - Neue Inhalationsstrategien
- **Perspektiven der Zukunft**
 - Neue Therapien
 - Forschung

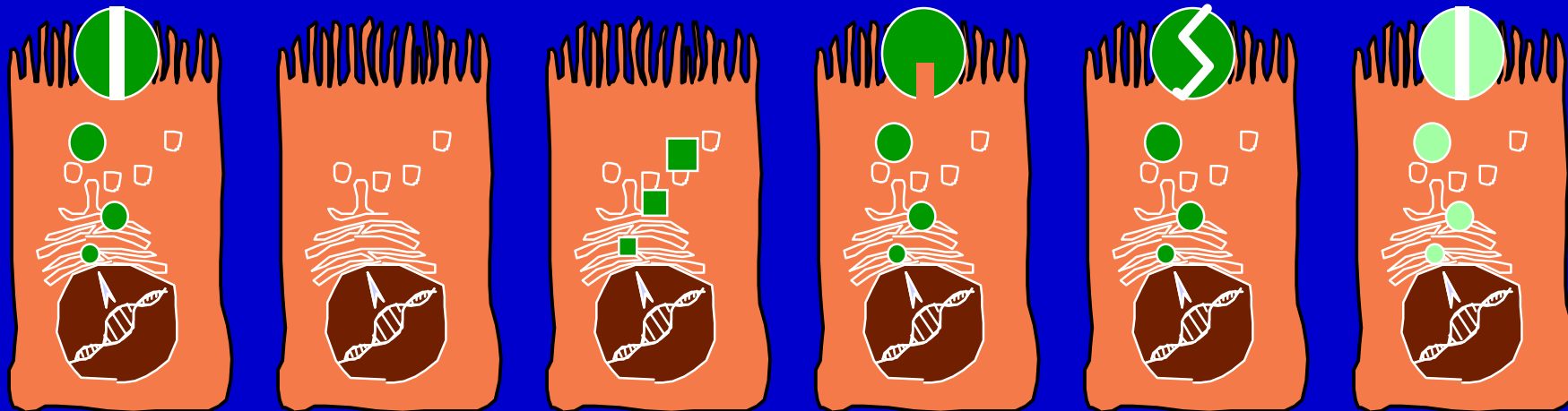
Cystische Fibrose (CF)

- Häufigste lebenserwartungsbeschränkende genetische Erkrankung der Kaukasier, aber weltweit vorkommend
 - > 30,000 CF-Pat in den USA
 - > 27,000 in Europa
 - USA: 1 in 2,500 Kaukasier; 1 in 17,000 Afro-Amerikaner
 - 1:3000 Neugeborene in Österreich (Screening)
- > 1500 Mutationen des Cystic fibrosis transmembrane regulator (CFTR) Gens;
defekter Ionentransport in Epithelzellen

Cystische Fibrose – eine Multiorganerkrankung

- meisten Organe betroffen
- Chronische (sino-)pulmonale Infektionen
- GI/Ernährungsstörungen/Leberzirrhose
- Männliche Infertilität (obstruktive Azoospermie)
- Erhöhter Kochsalzgehalt im Schweiß
- Lebenserwartung nimmt ständig zu;
- Sehr unterschiedlicher klinischer Verlauf möglich

Molecular Consequences of CFTR Mutations



Normal

I

II

III

IV

V

**No
synthesis**

**Block in
processing**

**Block in
regulation**

**Altered
conductance**

**Reduced
synthesis**

Nonsense
G542X

Missense

Missense
G551D

Missense
R117H

Missense
A455E

Frameshift
394delTT

AA deletion
ΔF508

Alternative
Splicing

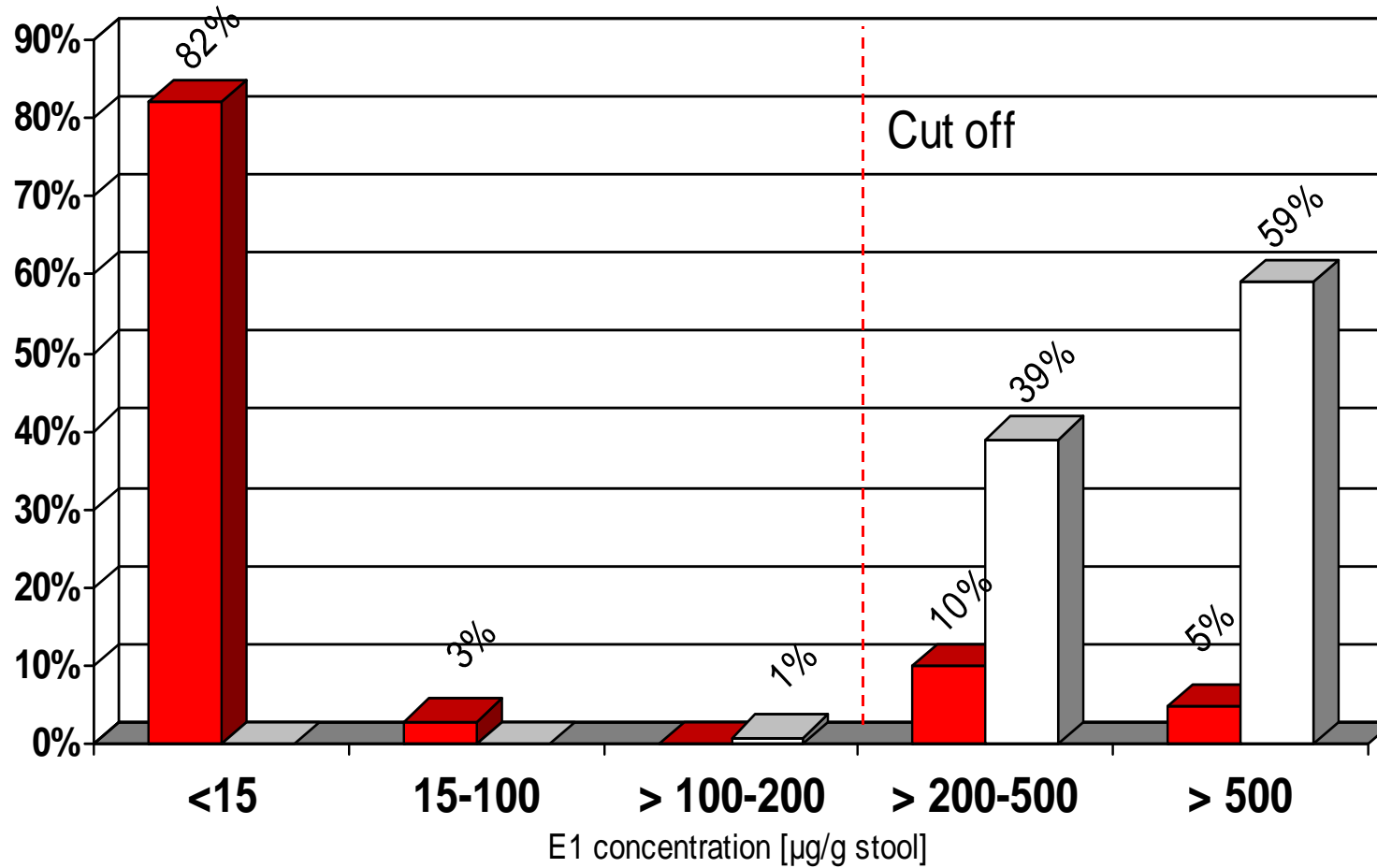
Splice junction
1717-1G→A

3849+10kbC→T

CF-Management

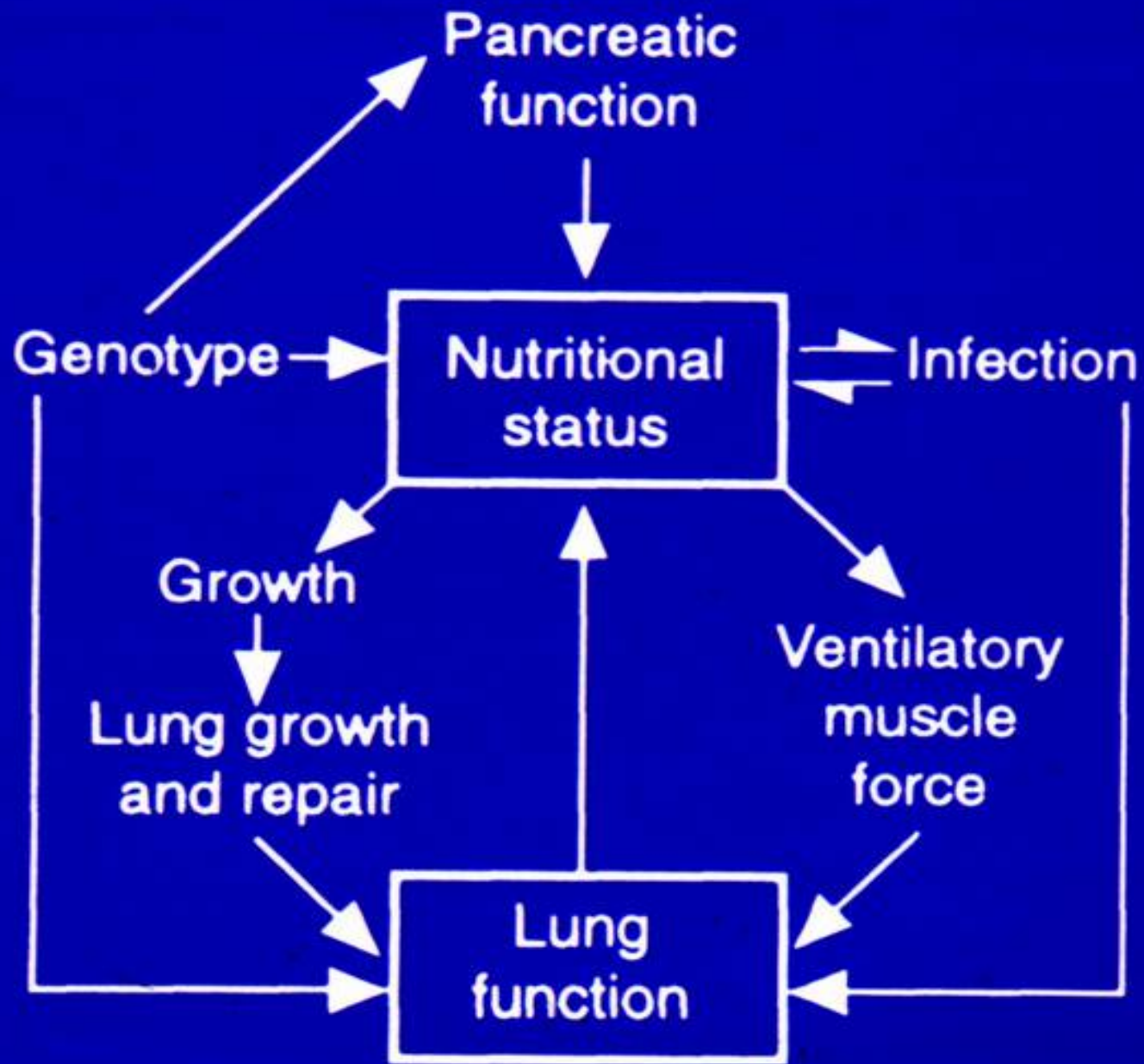
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Pancreatic Elastase-1 in CF-Patients



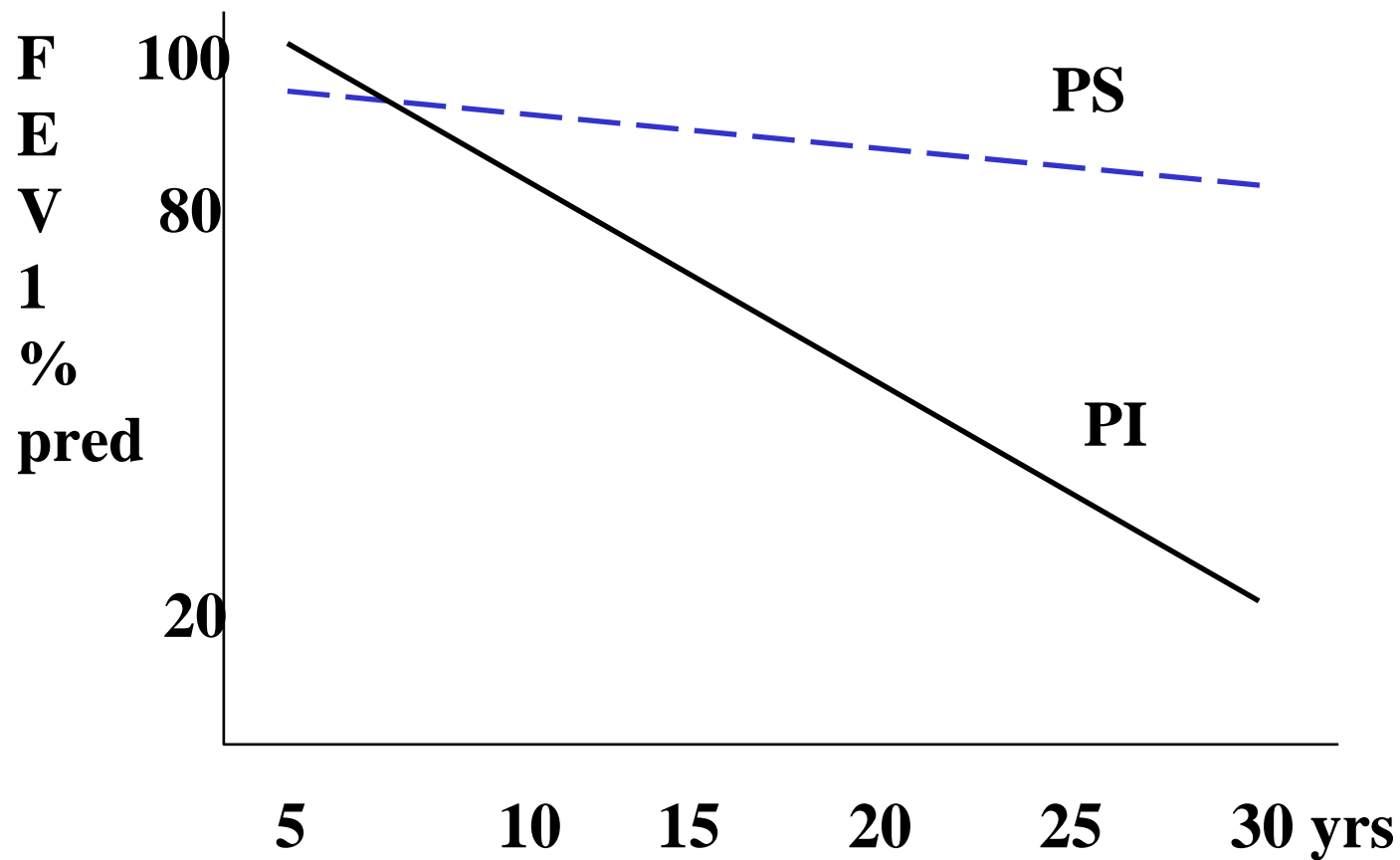
Terbrack et al. (1996)

■ CF-Patients (n=112) □ Controls (n=221)



FEV1 vs age in pancreatic in-/sufficiency

Corey J Pediatr 1997;131:809



Ernährungsstrategien

- Muttermilch
- Formula-milch ad libitum
- Positive Einstellung zum Essen
- Fettreich / Zwischenmahlzeiten
- 40 % Fett / 40% Kohlenhydrate / 20% EW
- Vitaminzufuhr incl Vit E 500 –1000 E /d
- 130-150 Kcal/kg/d (Sgl & Kl-kd)
- Enzyme !!

Meals vs. Enzyme supplements

- How much enzyme to overcome maldigestion/malabsorption ?
- Healthy adult: 30 000 U lipase/meal
- CF adult: 500-2500 U lipase /kg BW/meal
(enteric coated microspheres) (Consensus Committee 1995)
- no increase of enzymes >10 000 U lipase/kg BW
- consider other causes of maldigestion/malabsorption (CD, Colitis etc)

In children with CF, 94% of the parents interviewed reported that diet/mealtimes were a significant problem

In toddlers, specific problems noted:

48% Unwillingness by child to try new food

32% Child has poor appetite

33% Child would rather drink than eat

37% Parent feels anxious or upset at mealtimes

32% Parent not confident that child eats enough

26% Parent uses coaxing to get child to eat

(Powers et al., *Pediatrics*, 2002)

DiGirolomo, Quittner, & Winslow

Bronchopulmonary damage in CF

CFTR dysfunction

Sputum
specific antibodies

Viscous secretions
obstruction

elastase

Repair &
remodelling

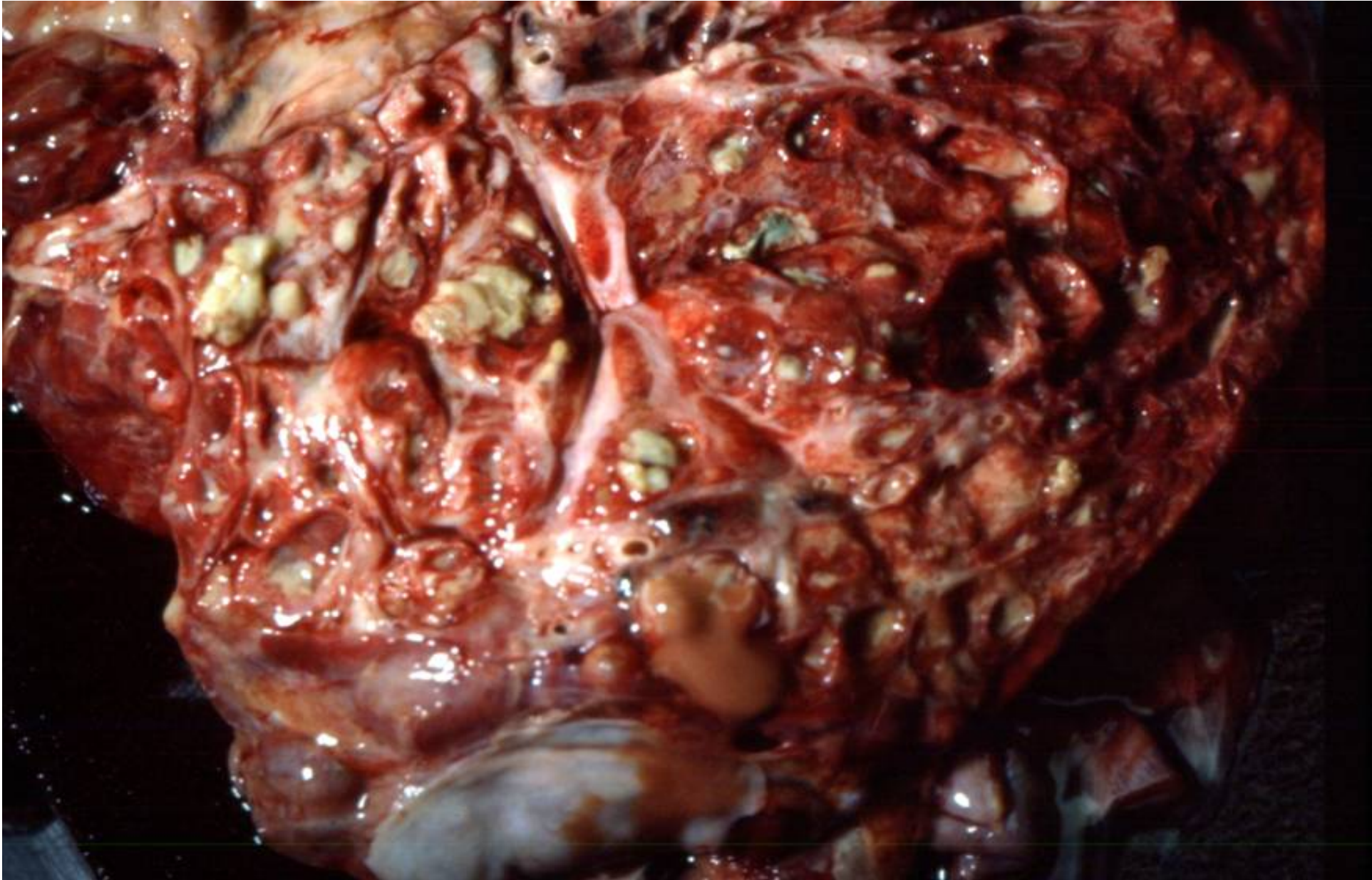
Bacterial Infection

Inflammation

IL-8

Lung damage
abnormal lung function

Death



DEC-1984
18:37.66
-MAY-1996
AGE 17

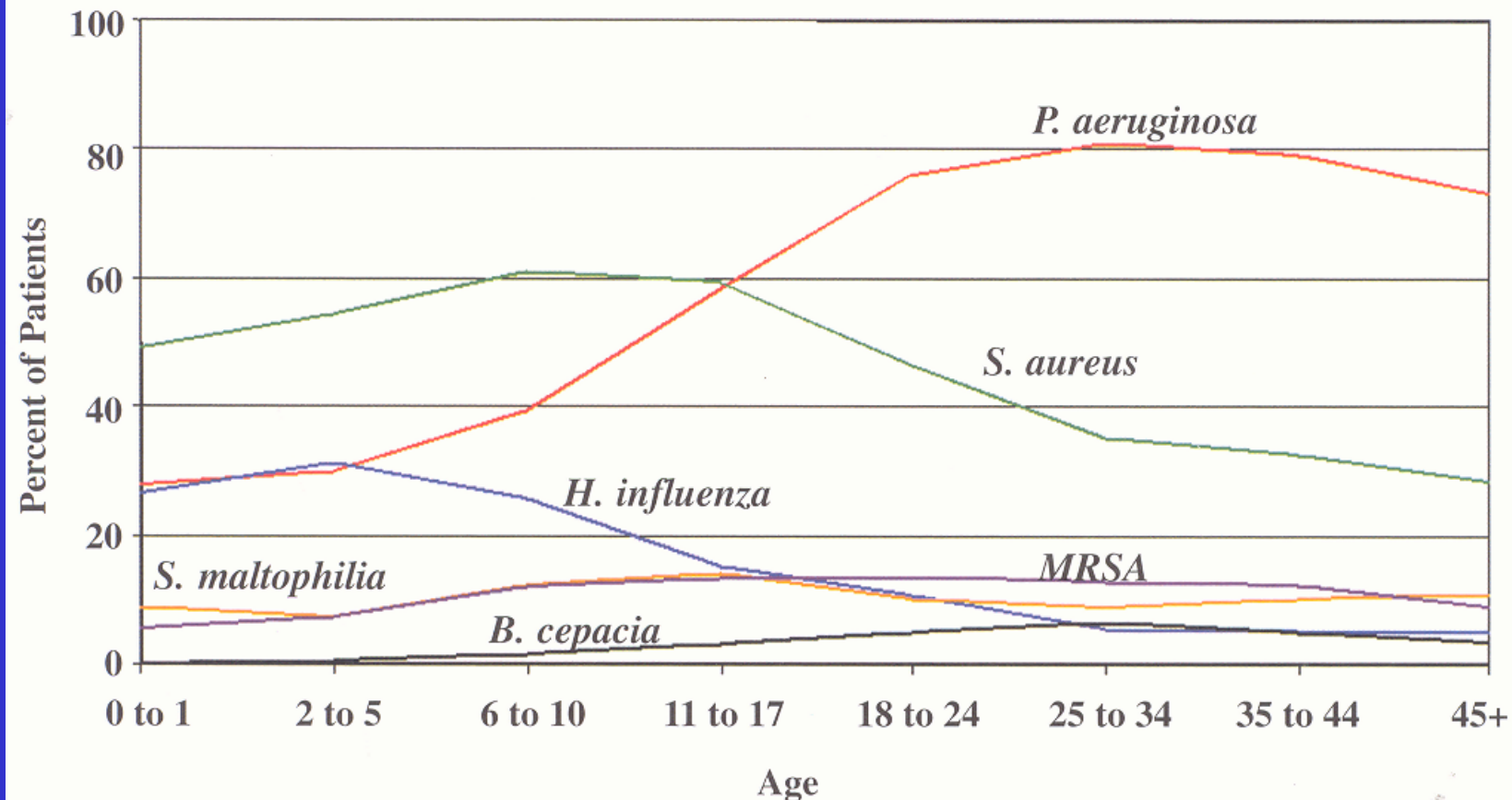
H-SP-CR

Q 17
553.5
2.0
0.75

10
C



Airway bacteriology in CF



Overall Percentage in 2003:

— <i>P. aeruginosa</i> 57.2%	— <i>S. aureus</i> 51.1%	— <i>H. influenzae</i> 16.8%
— <i>S. maltophilia</i> 11.0%	— <i>B. cepacia</i> 3.1%	— MRSA 11.8%

US CFF Registry 23000 pts 2004

Lungentherapie der CF

- Anti-infektiös
 - Tobii[®], Colistin, anti-Staph.
- Anti-inflammatorisch
- Anti-obstruktiv
 - rhDNase
 - Inhalierte HS
 - Thorax-PT

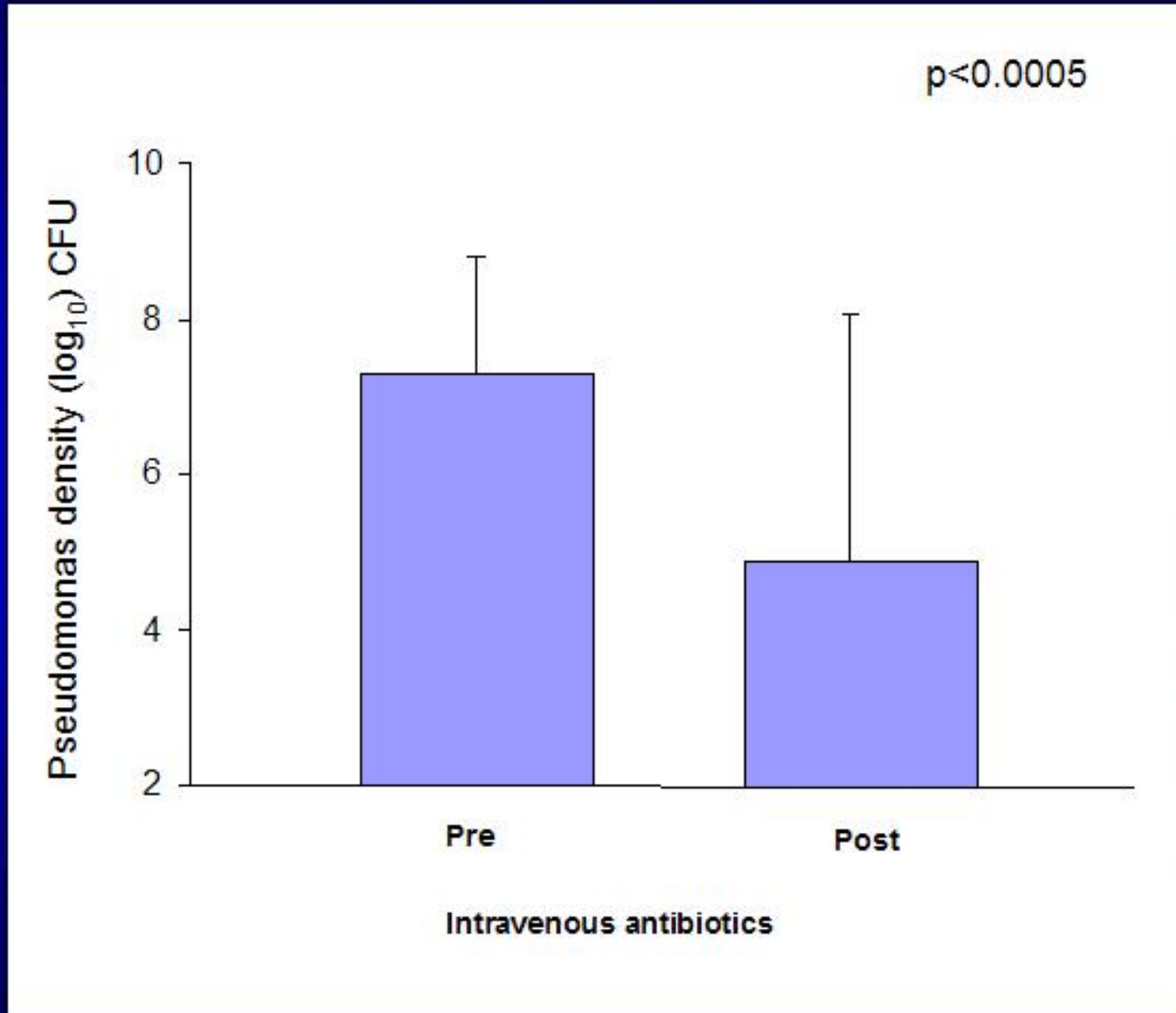
Nearly ALL therapy for CF is anti-inflammatory

- Chest PT
 - *Removes secretions*
- Antibiotics
 - *Fights infection*
- Nutrition
 - *Improves immunodefence*
- Lung transplantation
 - *Provides non-inflamed organ*

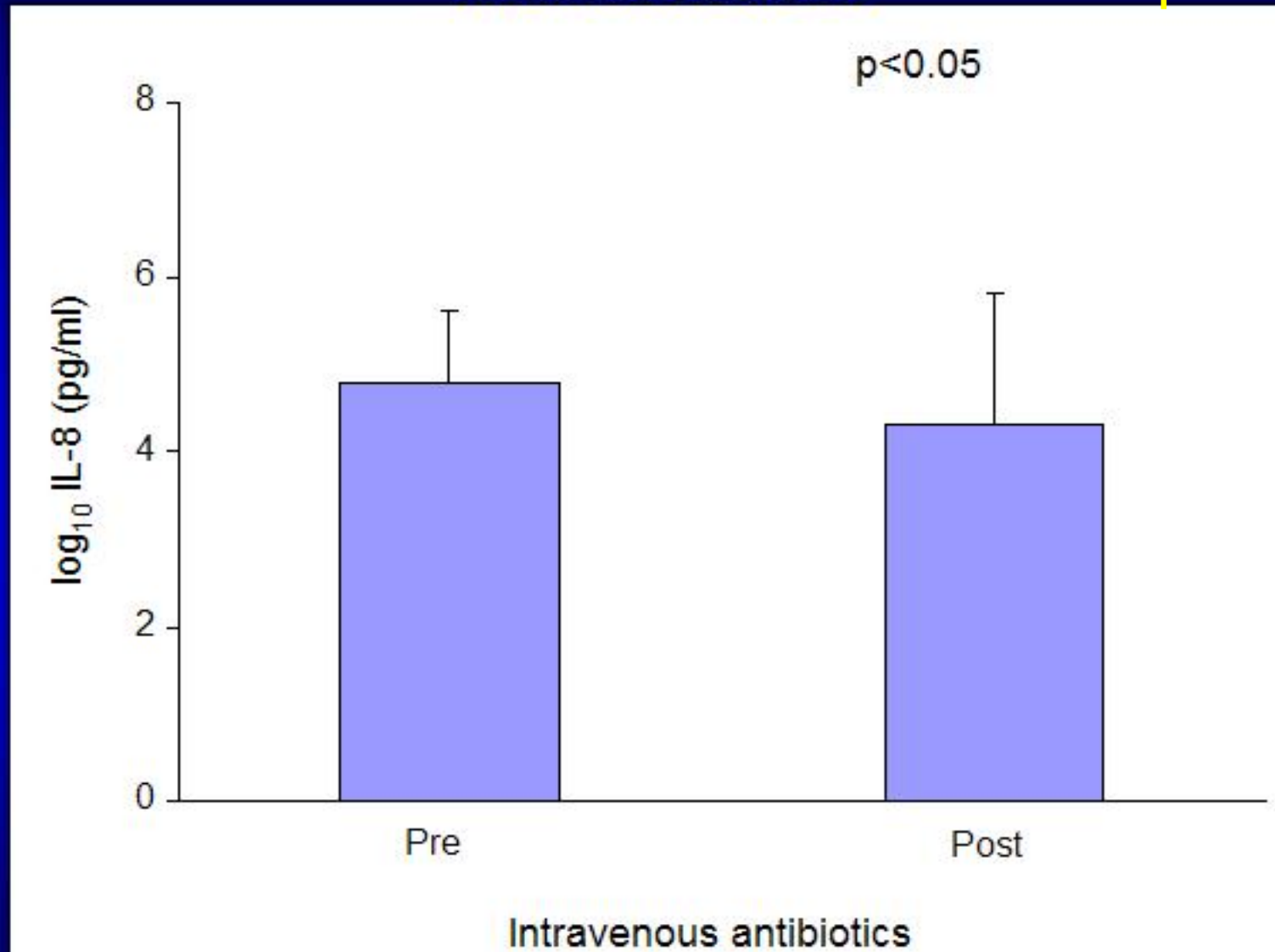
Antibiotikaaanwendung bei CF bei/als

- **akuten** Exazerbationen i.v.
- **chronisch** suppressive Therapie
 - oral
 - inhalativ
 - regelmäßige IV Therapie („dänisches Modell“)
 - Heimtherapie
- **Initial**therapie bei *P.aeruginosa*

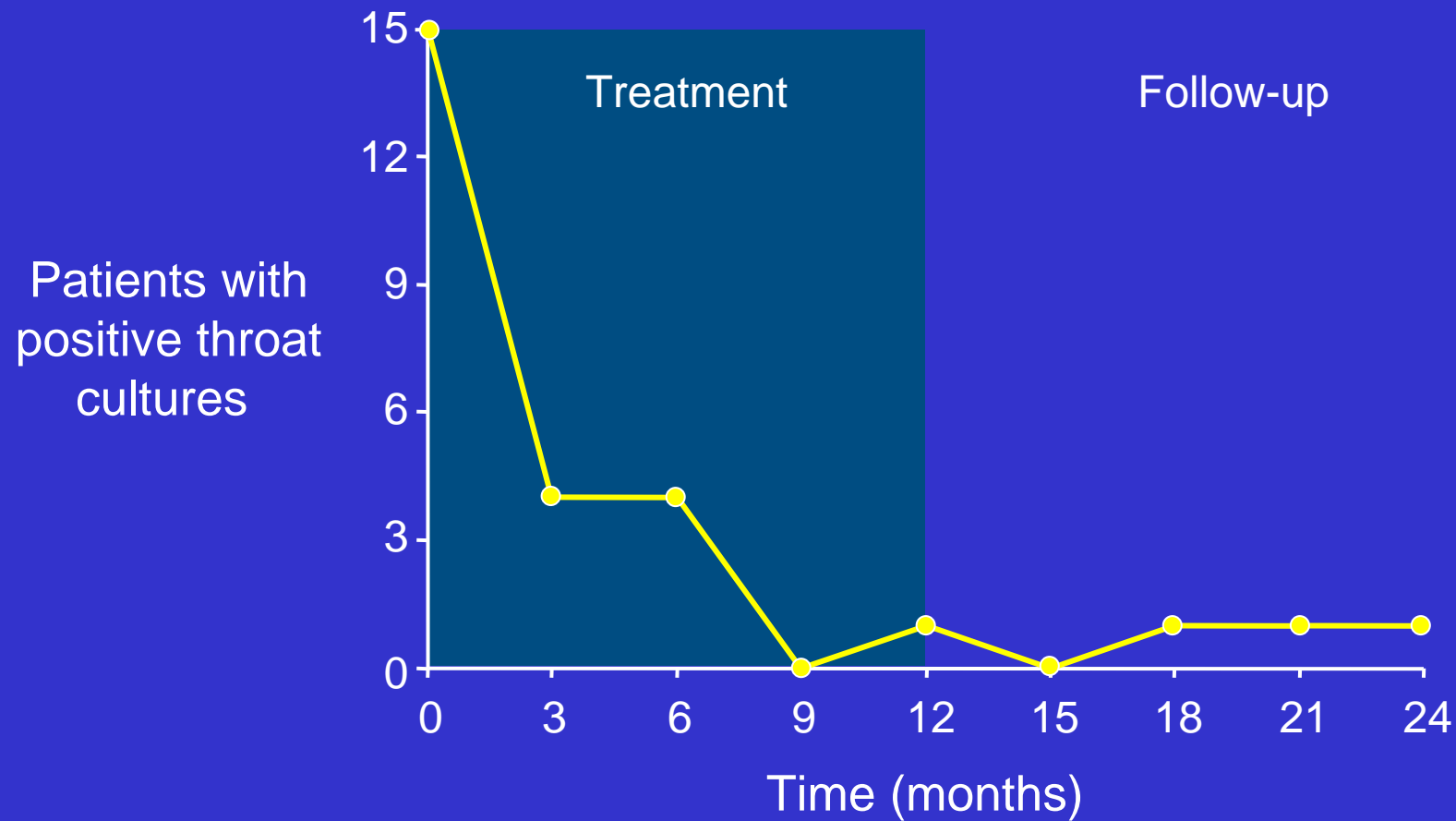
Bacterial burden after antibiotics



Inflammation markers post ABs



Delay of *P. aeruginosa* Colonization: Inhaled Tobramycin



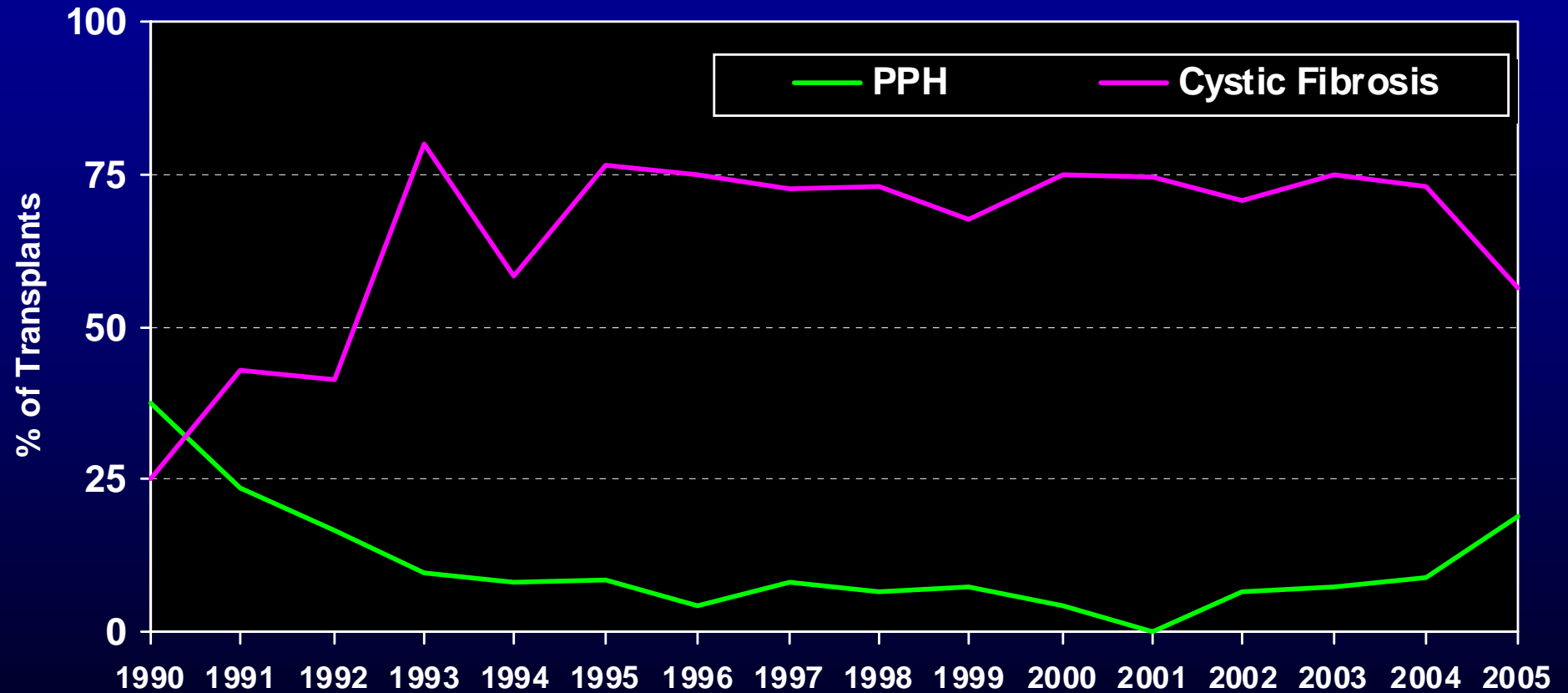
Ratjen et al., Lancet 2001;358:983-4

Sport als Physiotherapie-alternative

- Verminderter Lungenfunktionsabfall
- Vermehrte Sekretexpektion
- Langzeitkonzept erforderlich
- Wohlbefinden deutlich besser
- Konsequenz: Sport und körperliche Aktivität früh in Alltagsleben einplanen

DIAGNOSIS IN PEDIATRIC LUNG RECIPIENTS BY YEAR OF TRANSPLANT

Age: 12-17 Years



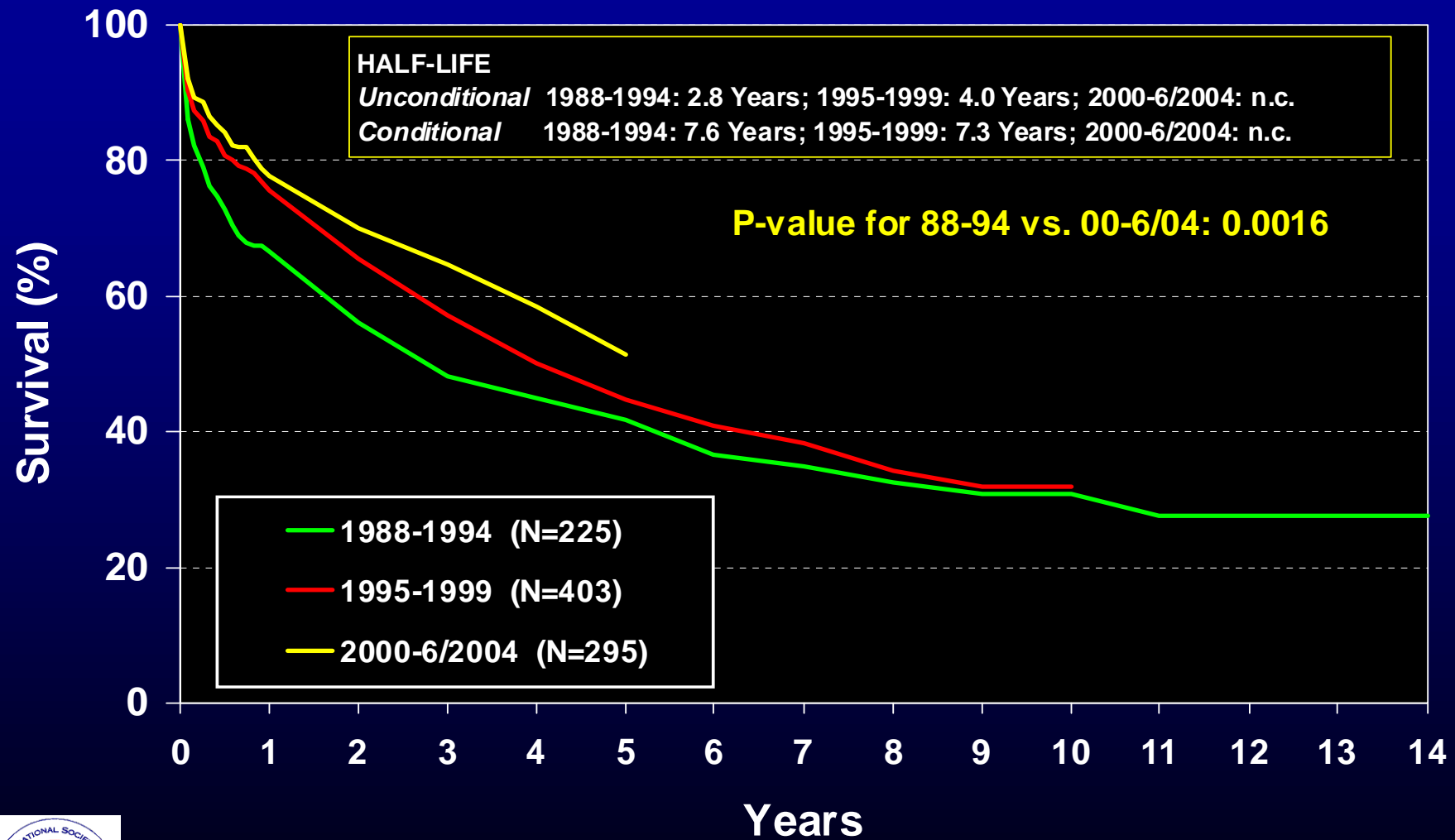
ISHLT

2006

J Heart Lung Transplant 2006;25:904-911

PEDIATRIC LUNG TRANSPLANTATION

Kaplan-Meier Survival by Era (Transplants: January 1988 - June 2004)



ISHLT

2006

J Heart Lung Transplant 2006;25:904-911

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Antiinflammatory CF drug treatments

- Corticosteroids
- Non-steroidal anti-inflammatory agents
- Macrolides
- rhDNase (also a mucolytic)

- Antiproteases
- Antileukotrienes

Oral corticosteroids: effective, but serious side effects (growth, cataract, osteoporosis)

(Auerbach 1985; Eigen et al. 1995; Henderson et al 1999; Lai et al. 2000)

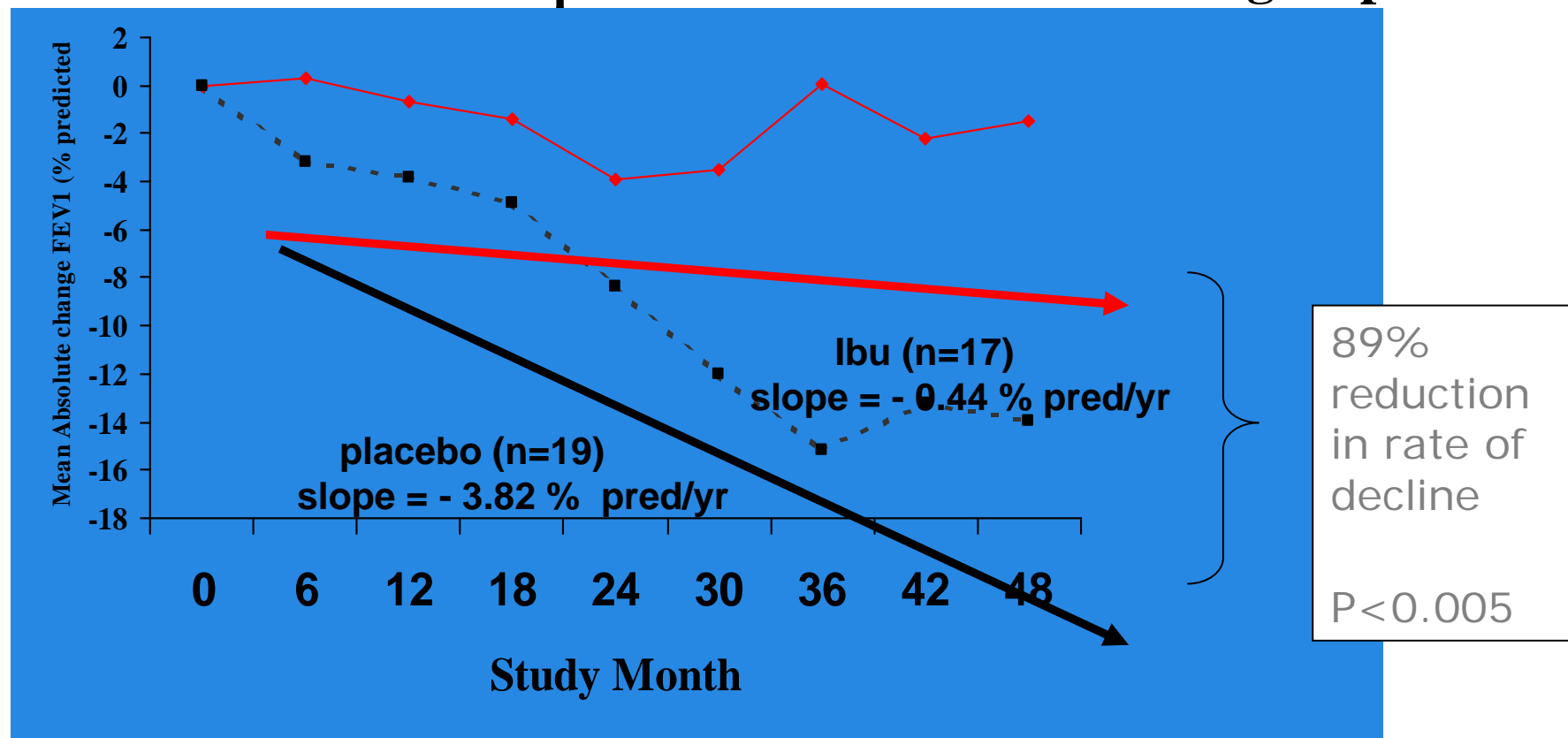
Inhaled corticosteroids: effective?

(Schjøtz et al 1983; Dezateux et al. 2000; Wojtczak et al 2001; Balfour-Lynn Cochrane Review 2004, issue 4; Balfour-Lynn et al AJRCCM 2006)

Steroids – new approaches: infusion of autologous erythrocytes loaded with

dexamethasone *Lucidi BMC Pediatr. 2006 May 24;6(1):17*

Effect of Ibuprofen on Annualized Rate of FEV₁ Decline 5-13 Yr Old Subgroup



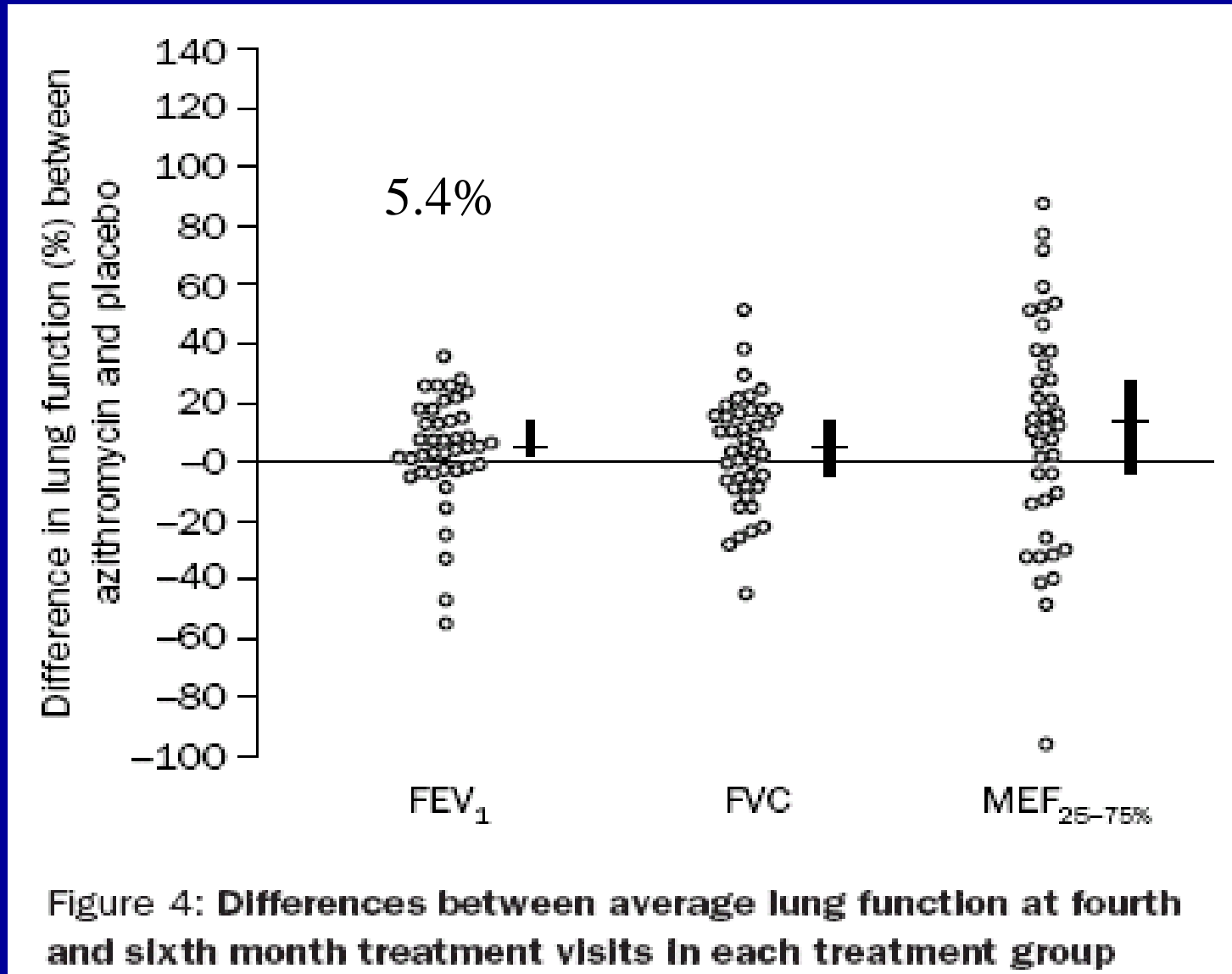
Ibuprofen: slower annual decline of FEV₁ only in a subgroup of patients (< 13 years)

M Konstan et al, NEJM 1995; 332:848, Chest. 1999 Apr;115(4):1053-8 1999)

Macrolides - mode of action ?

- Treatment of occult *Staph. aureus* or *H. Influenzae* or NTM infection?
- Anti-viral properties ??
- suppress production of proinflammatory cytokines IL-6, IL-8, TNF α
- effects on *Ps. aeruginosa* exoproducts & biofilm formation

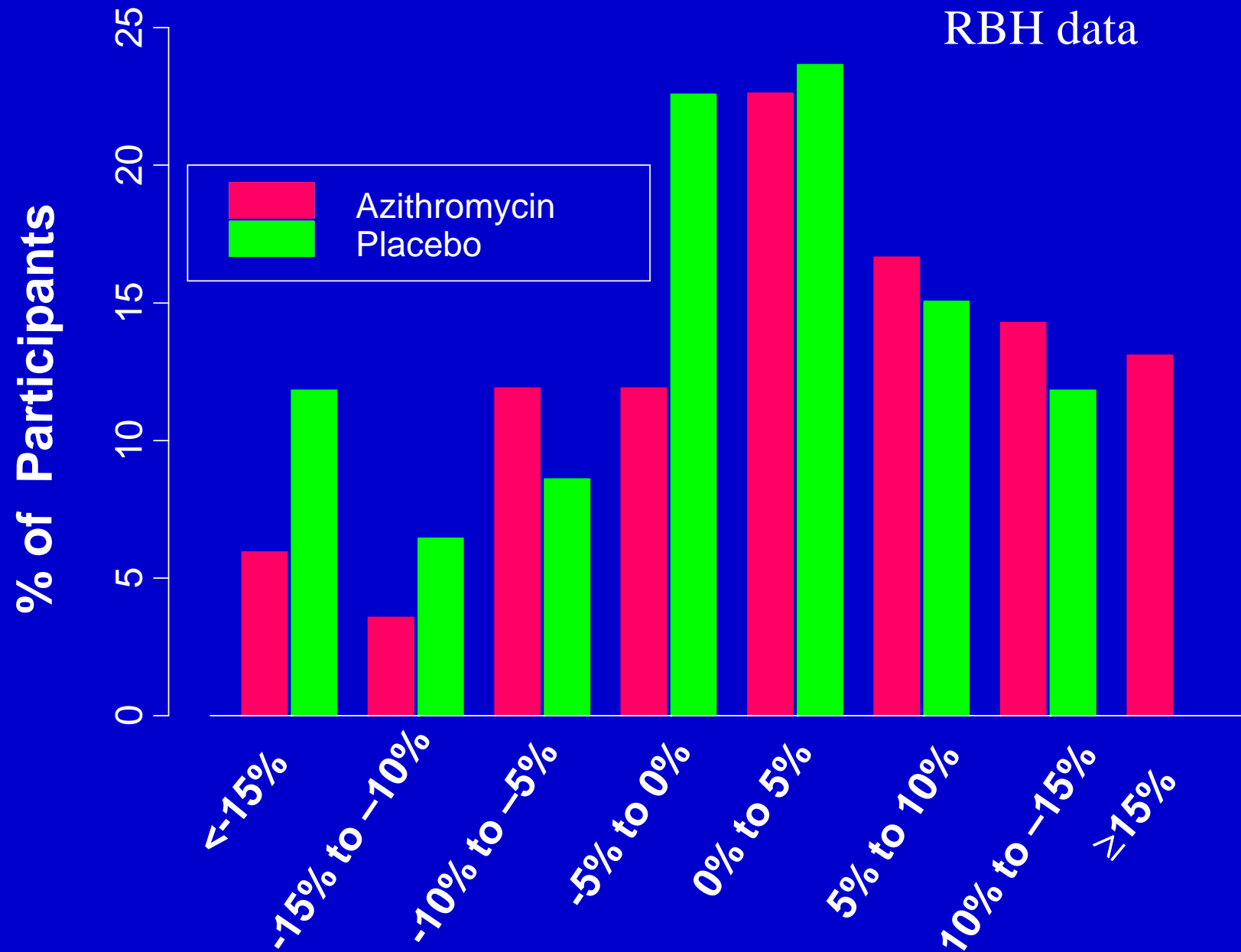
Long term azithromycin in CF; n=41; 8-18 yrs; UK



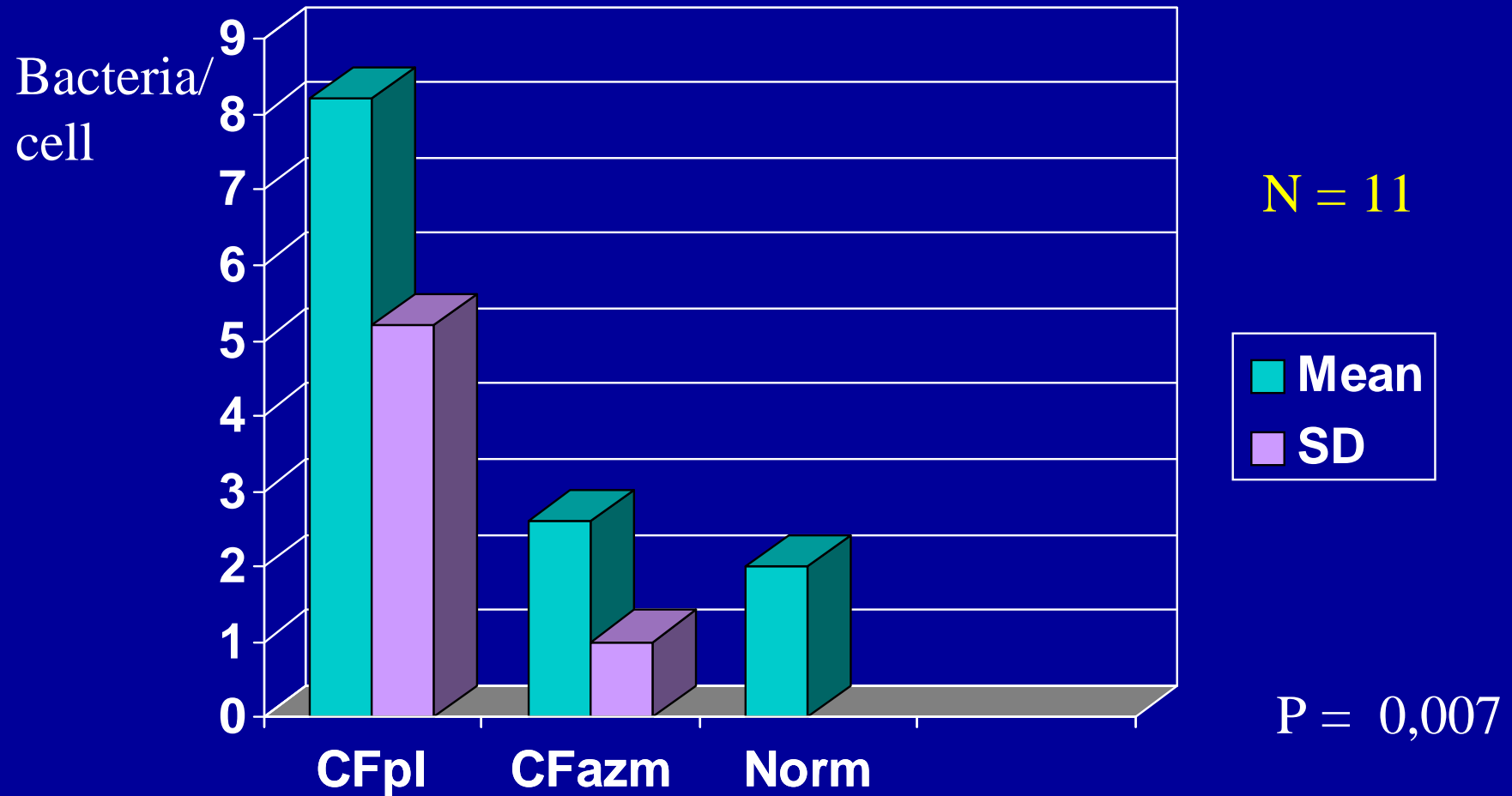
R DB PC CO 15 mo

Equi et al Lancet 2002;360:978

168-Day Relative Change in FEV₁ % Predicted



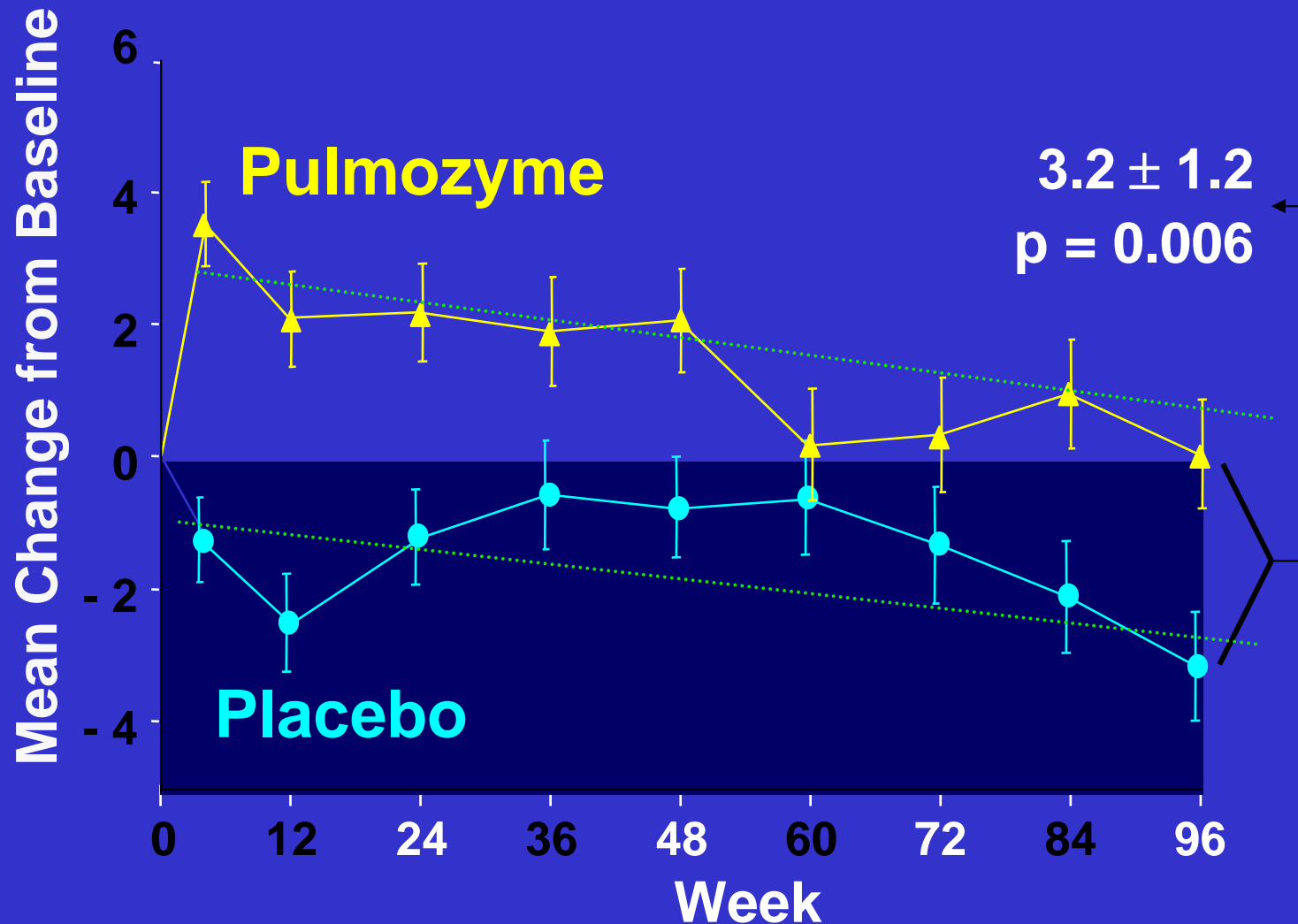
Azm and *Ps Aer.* adherence



Baumann U et al Infection. 2001 Jan-Feb;29(1):7-11.

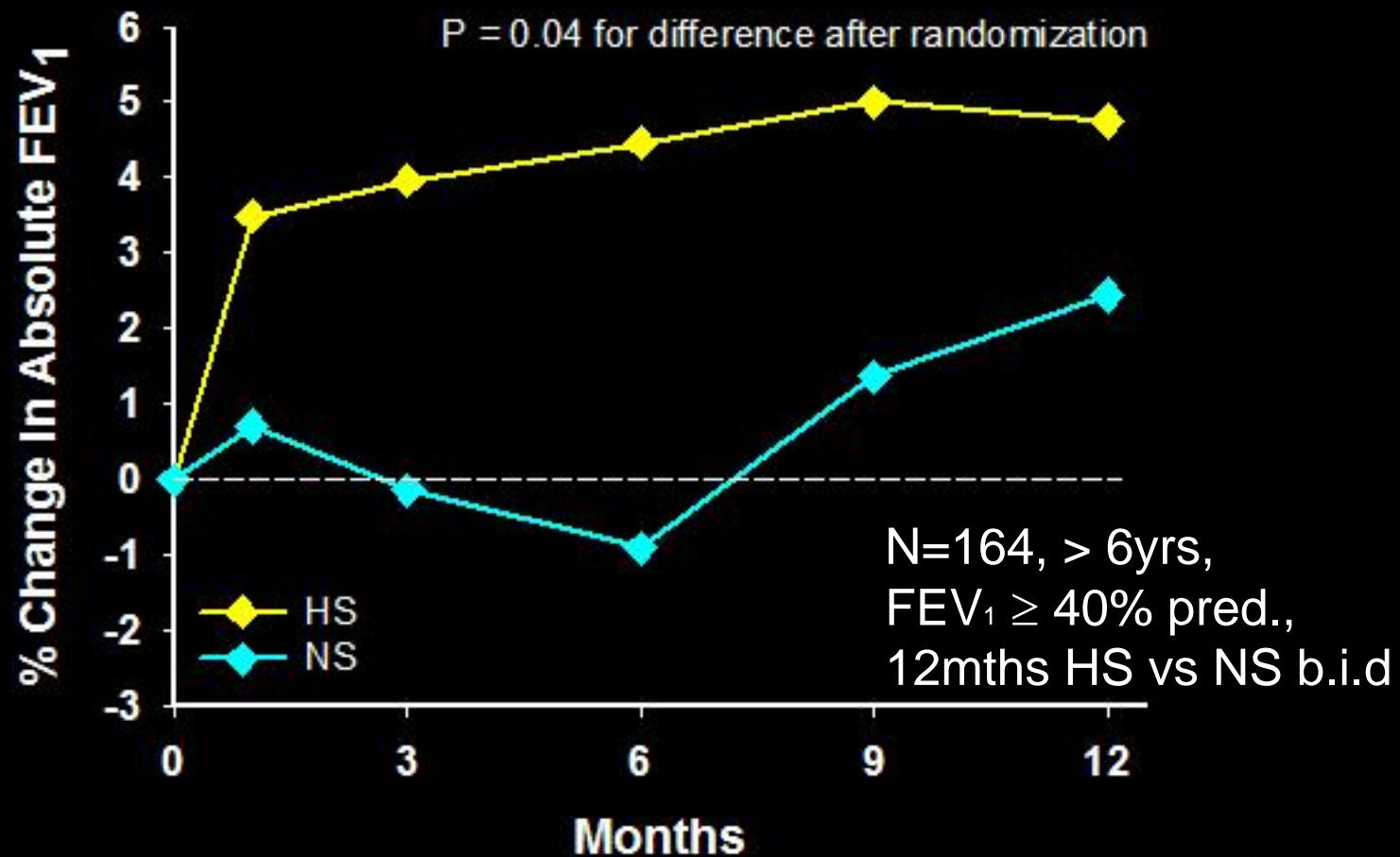
Pulmozyme Early Intervention Trial

Change in FEV₁ % Predicted

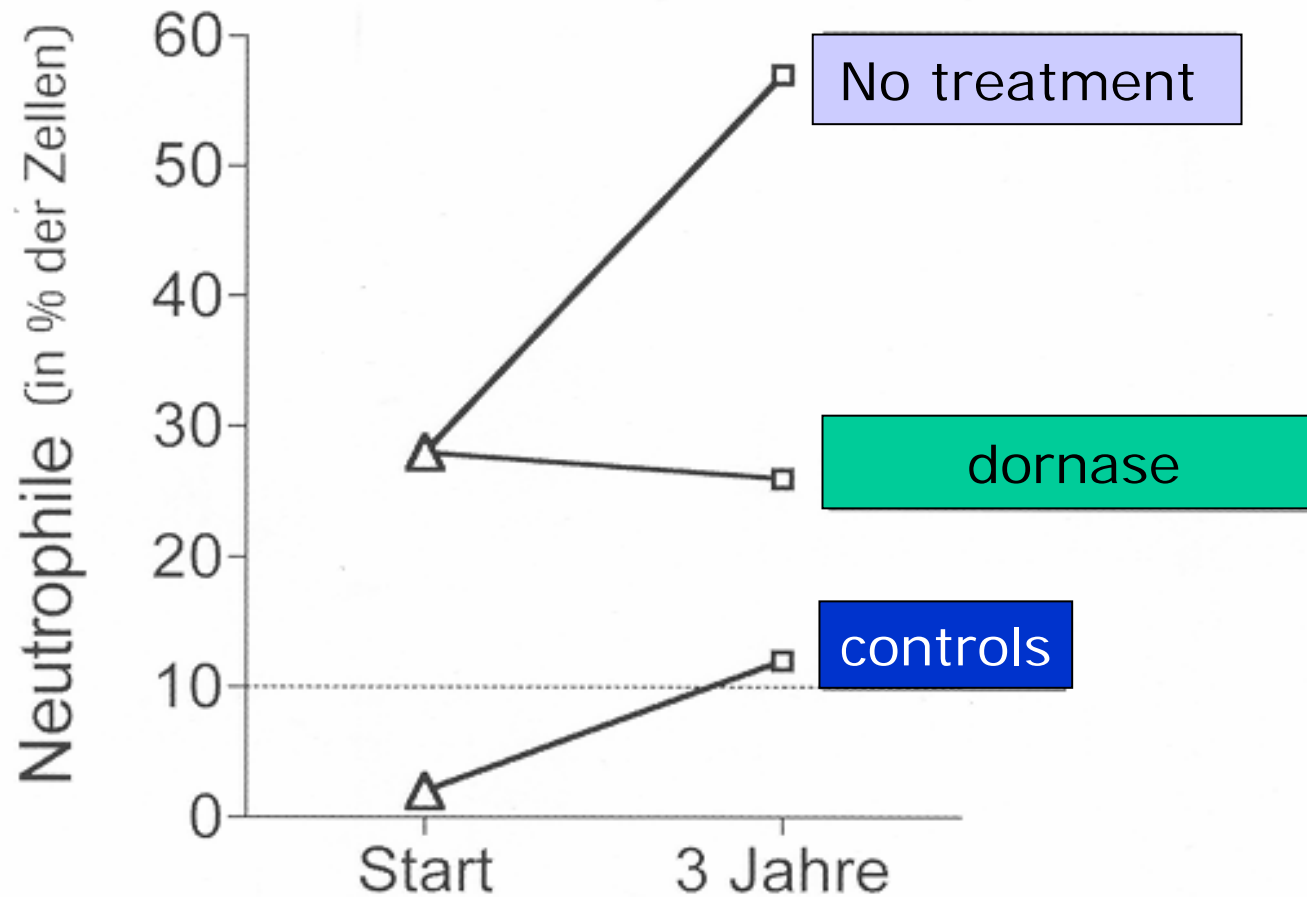


Australian National HS Trial - Results

Percent Change in Absolute FEV₁



Effect of 2.5 mg Dornase α /d on **airway inflammation** in 105 German pts with CF:



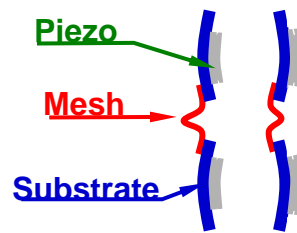
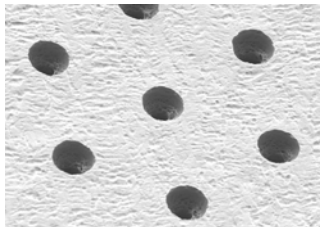
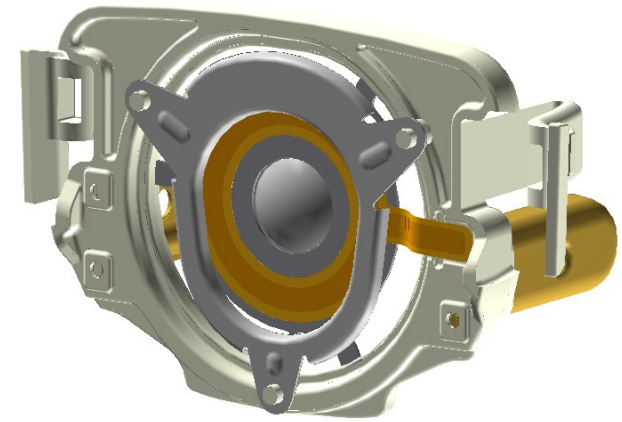
Paul et al AJRCCM 2004; 169; 719

AIS Delivery System: eFlow™ Electronic Inhaler (PARI)

- Small, portable, battery operated nebulizer/inhaler unit
- Perforated stainless steel membrane aerosol generator
- Relatively monodispersed particle spectrum
- Whole lung deposition ~41% of emitted dose
- Delivers dose ~ 4x faster than PARI LC Plus

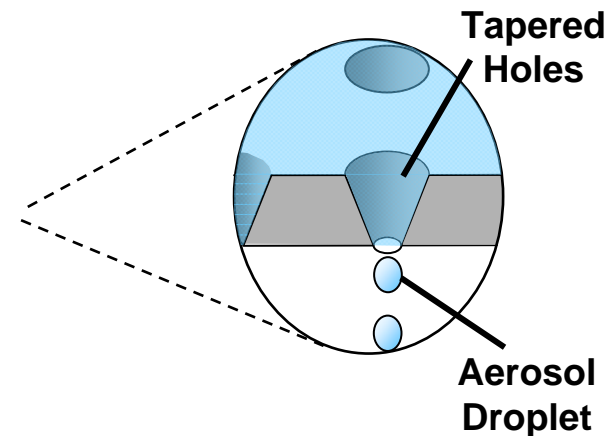


Technisches Prinzip der Membranvernebler



Vibration

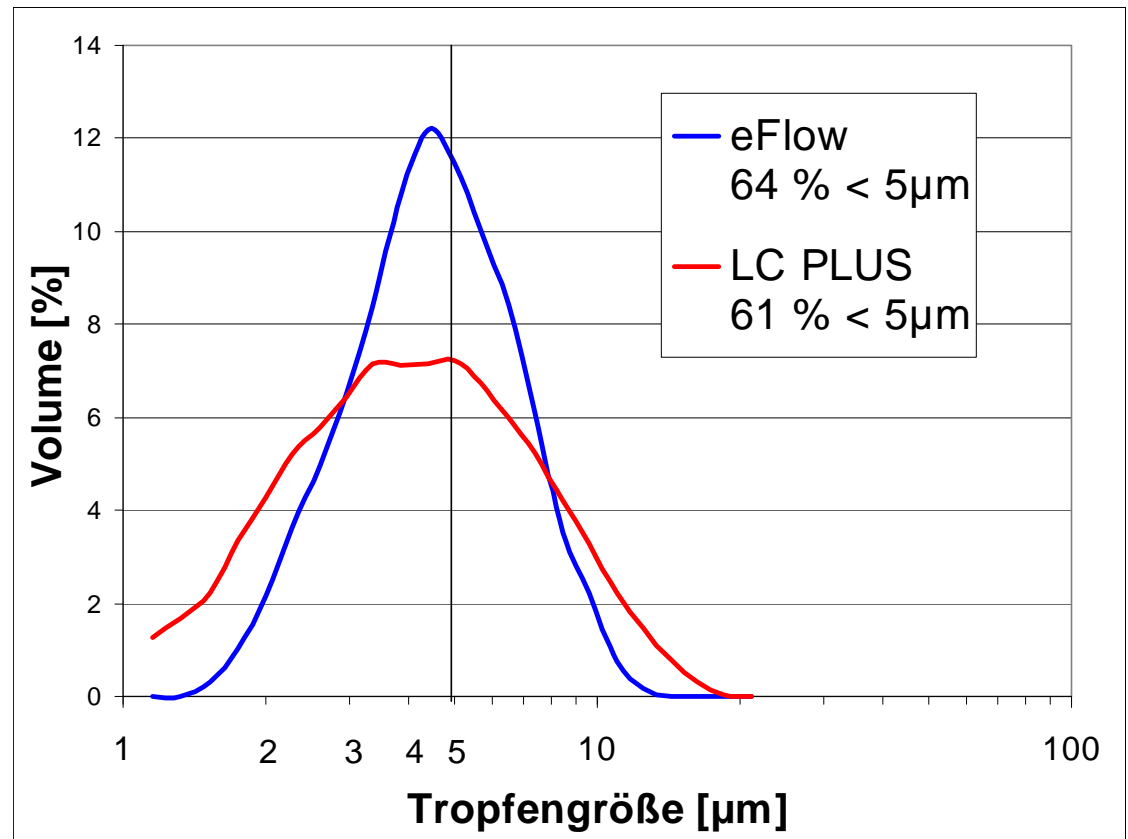
(Patent protected US
5,518,179)



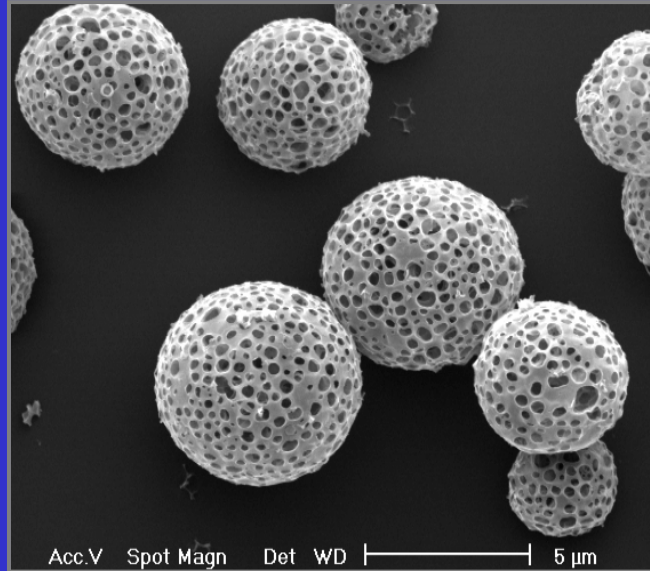
Vorteile der Membranvernebler

maßgeschneiderte Tropfen

- Anteil $< 5\mu\text{m}$ entspricht LC PLUS
- enge Größenverteilung
- mögliche Tropfengröße 2.5 bis $> 5\mu\text{m}$ je nach Membran und Anwendung



Dry Powder Inhaler Tobramycin Development



- Spray-dried tobramycin powder for inhalation, supplied in dose capsules
- Powder formulation: tobramycin sulfate, distearoylphosphatidylcholine, calcium chloride: water and perflubron as residual processing agents



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Neue CF Therapien

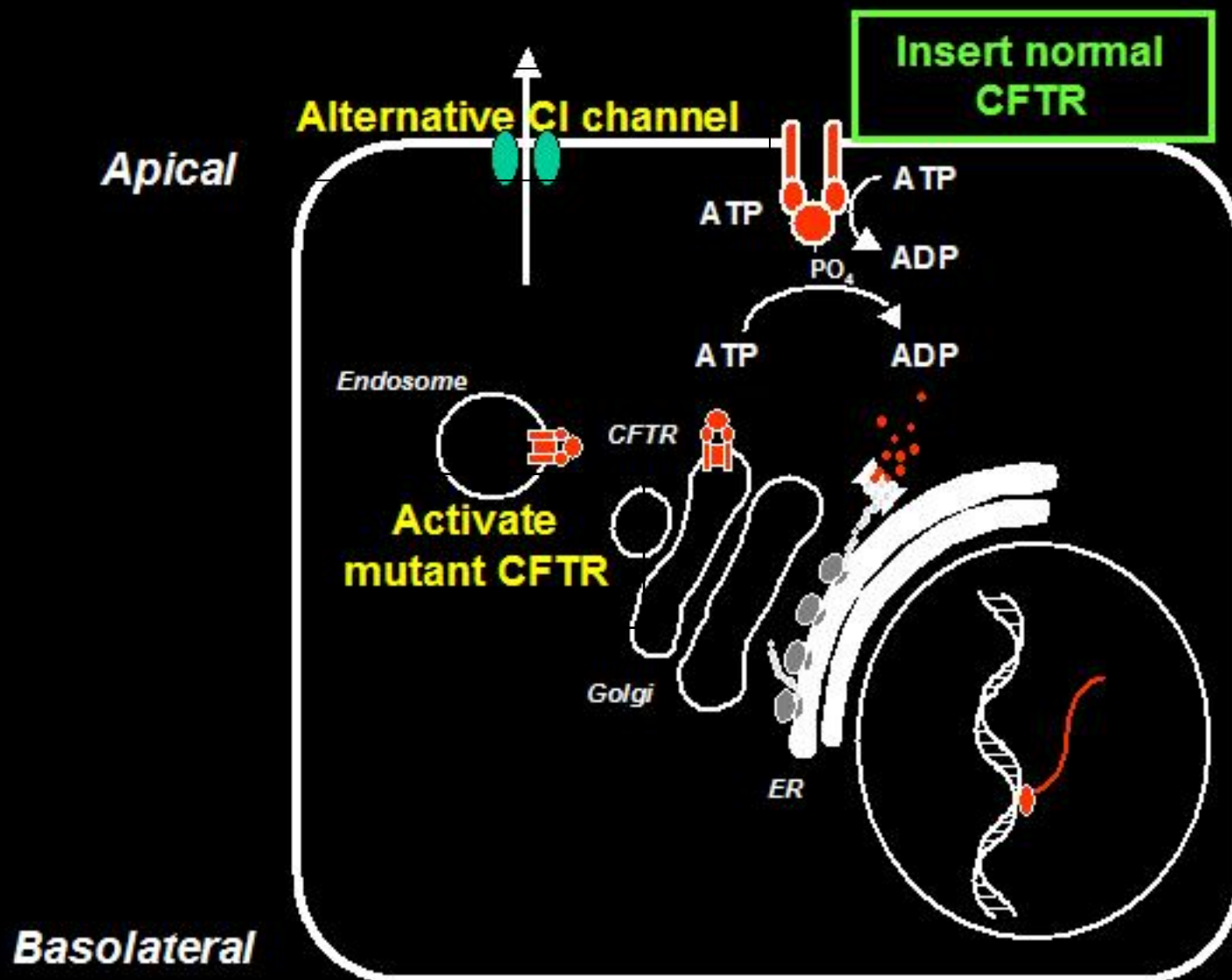
- rekombinante Enzyme
- Wachstumshormon
- Insulin
- Inhaliertes L-Arginin
- Inhaliertes Xylitol
- neue
Beatmungstechniken
(NIPP, Bi-PAP)

- Alpha-1-antitrypsin
- SLPI
- IL-10 i.m. (Mäuse)
- Interferon

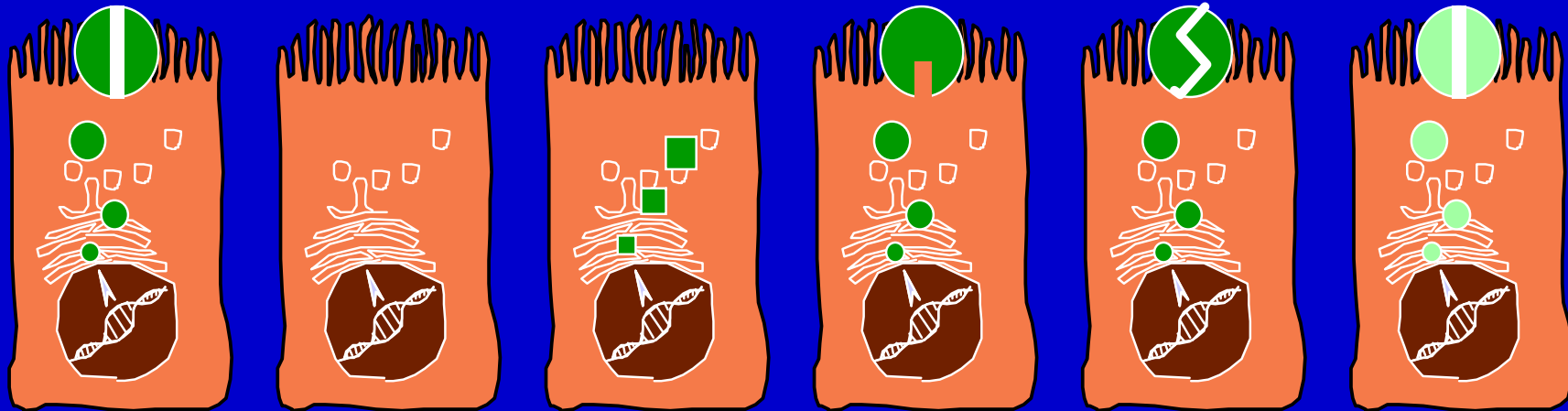
„basic science „ - Perspektiven der Zukunft

- Gentherapie
- Pharmakolog. CFTR Korrektur
- Künstliche Chromosomen
- Stammzellentherapie

Addressing the Basic Defect in CF



Molecular Consequences of CFTR Mutations: potential therapies



Normal

I

II

III

IV

V

No
synthesis

Block in
processing

Block in
regulation

Altered
conductance

Reduced
synthesis

aminoglycosides

alkylxanthines;
genistein

splicing
factors

phenylbutyrate

CFTR
phosphorylation

Research	Preclinical	Phase 1	Phase 2	Phase 3	Patient
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Compacted DNA

Gene therapy

PTC124

Curcumin

Vertex Potentiator

Protein repair

GSHO

Vertex Corrector

UCSF

Denufosol

Salt transport

SPI-8811

Parion 552-02

Moli1901

INO 4995

PULMOZYME

HYPERTONIC SALINE

Mucus

Lomucin

DHA

Oral N-acetylcysteine

Inhaled Nacystelyn

Anti-inflammatory

Hydroxychloroquine

Low-dose Methotrexate

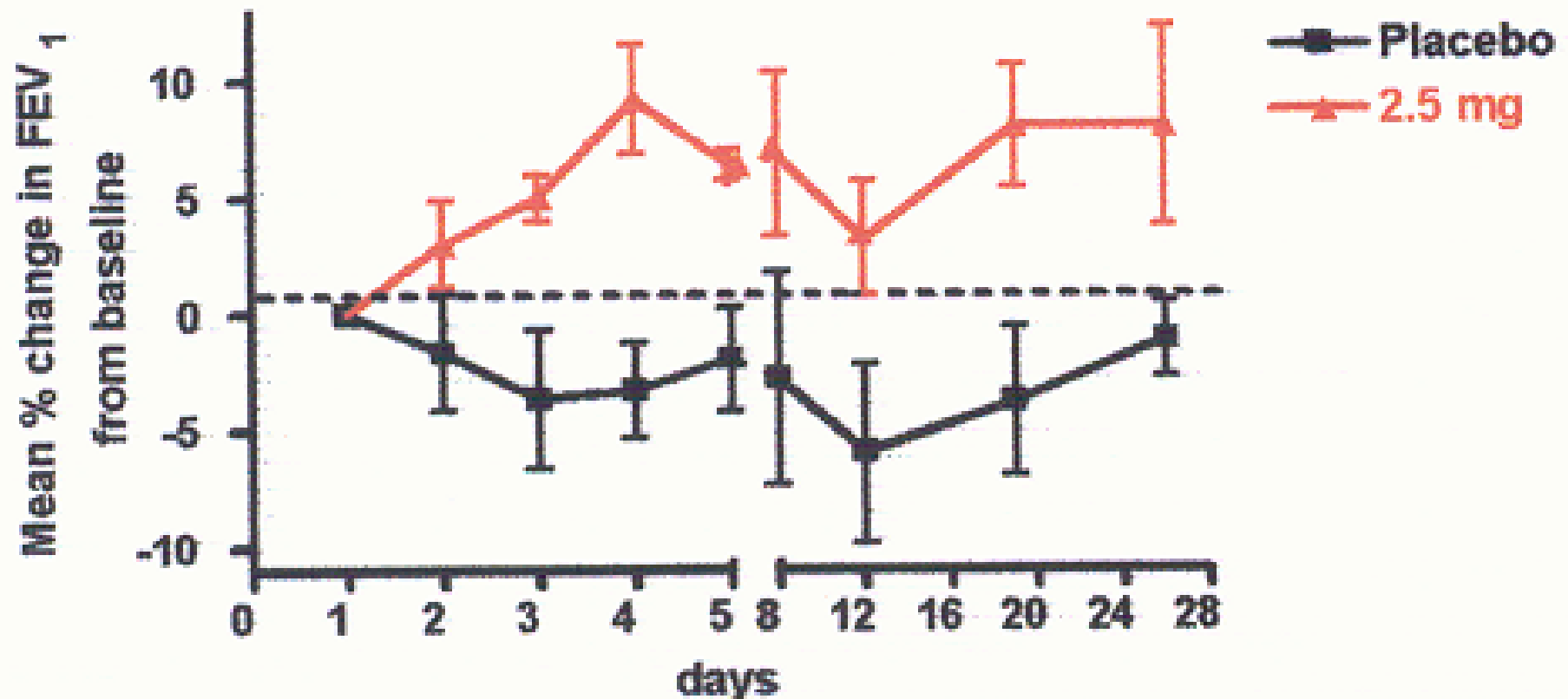
Pioglitazone

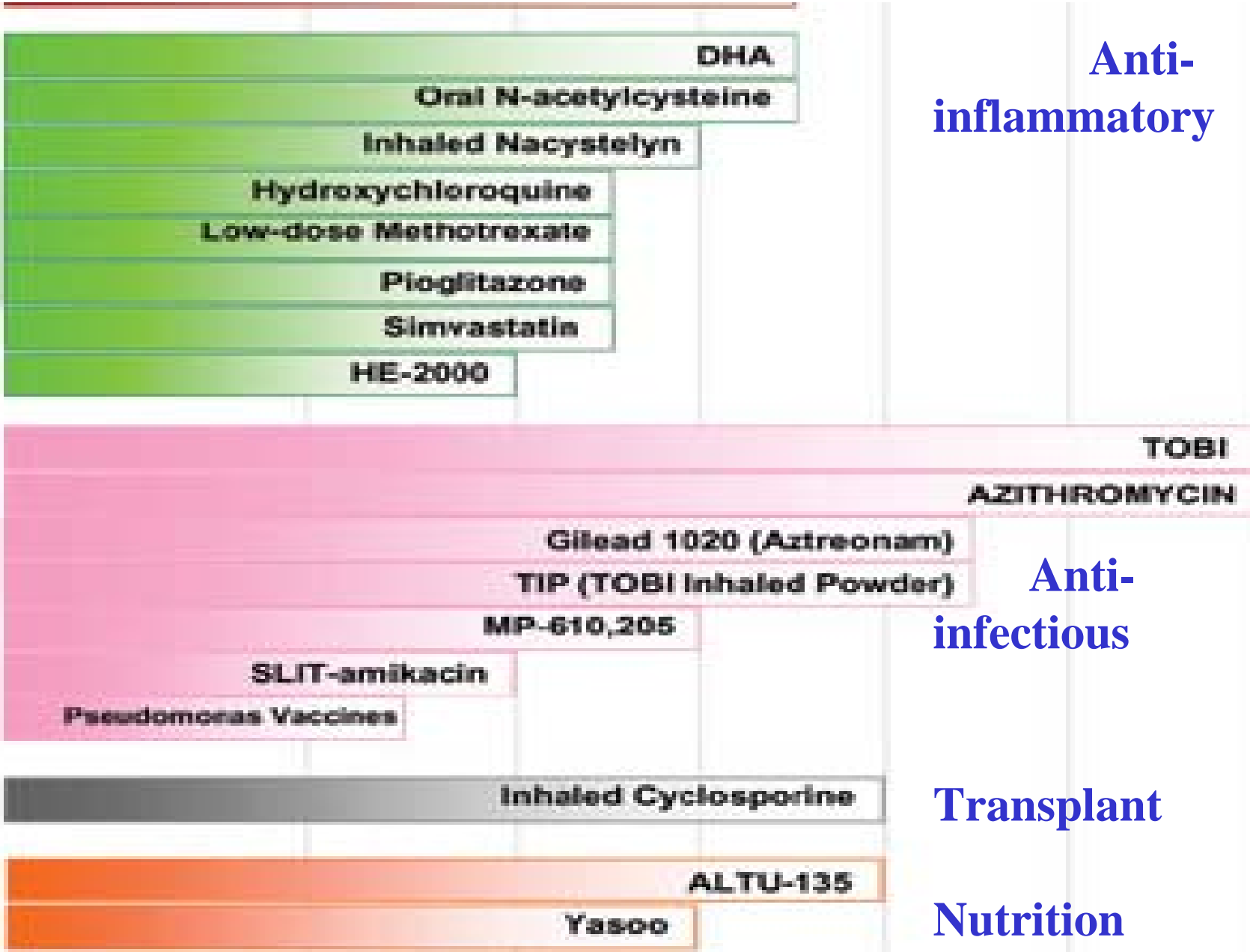
Simvastatin

HE-2000

Inhalation von Moli1901 bei Pat mit CF

Grasemann et al Chest 2007 in print





Res'ch	Preclin.	Phase 1	Phase 2	Phase 3	Patient

Der „gesunde“ CF Patient

- Optimierte Ernährung
- Körperliche Aktivität ++; PT ?
- Alle Impfungen
- Infektionsbehandlung
 - Präventiv ?, nach Bedarf ?
- Genaue Observanz
- Zukunftsperspektiven ?





CF Basistherapie

- Pankreasenzymzufuhr
- Hochkalorische Ernährung
- Spezialisierte Thoraxphysiotherapie
- Körperliche Aktivität
- Antiobstruktive antiinfektiöse
antiinflammatorische Pharmakotherapie
 - Pulmozyme TOBI, Azithromycin

Pancreas associated issues

- Basics:** # pancreatic insufficiency present in >85% of CF
- # malnutrition determines survival and quality of life
 - # optimal energy input PLUS enzyme supplements to avoid malnutrition
 - # supplementation far from ideal
 - # complete correction of malabsorption not achievable

newer established treatments

- Dornase (Pulmozyme ®) early intervention
 - » Paul et al AJRCCM 2004;169:719
 - » Ratjen et al Pediatr Pulmonol. 2005;39(1):1-4
 - *Hypertonic saline ??*
- Tobramycin (TOBI®) inhalation
 - » Ramsey et al N Engl J Med 1999;340:23
 - » Moss Chest. 2002;121(1):55-63.
- Antibiotic prophylaxis ????
- » Stutman et al J Pediatr 2002;140:299 *cephalexin*
- » Equi et al Lancet 2002;360:978 *azithromycin*
- Antiinflammatory agents
 - » Konstan et al N Engl J Med. 1995;332:848
 - » Konstan et al J Pharmacol Exp Ther. 2003;306:1086

Perspectives: CF pulmonary disease

Pathogenesis

Genetic and protein defect

Abnormality in salt and water transport

Poor mucus clearance

Persistent airway infection

Chronic Inflammation

Exacerbations of infections

Airway Obstruction

Progressive lung destruction

Early Death

Clinical Trials

Gene Transfer
Chaperones

Ion Transport
Regulators

Chest PT
Mucolytics

Early Antibiotics
Vaccination ???

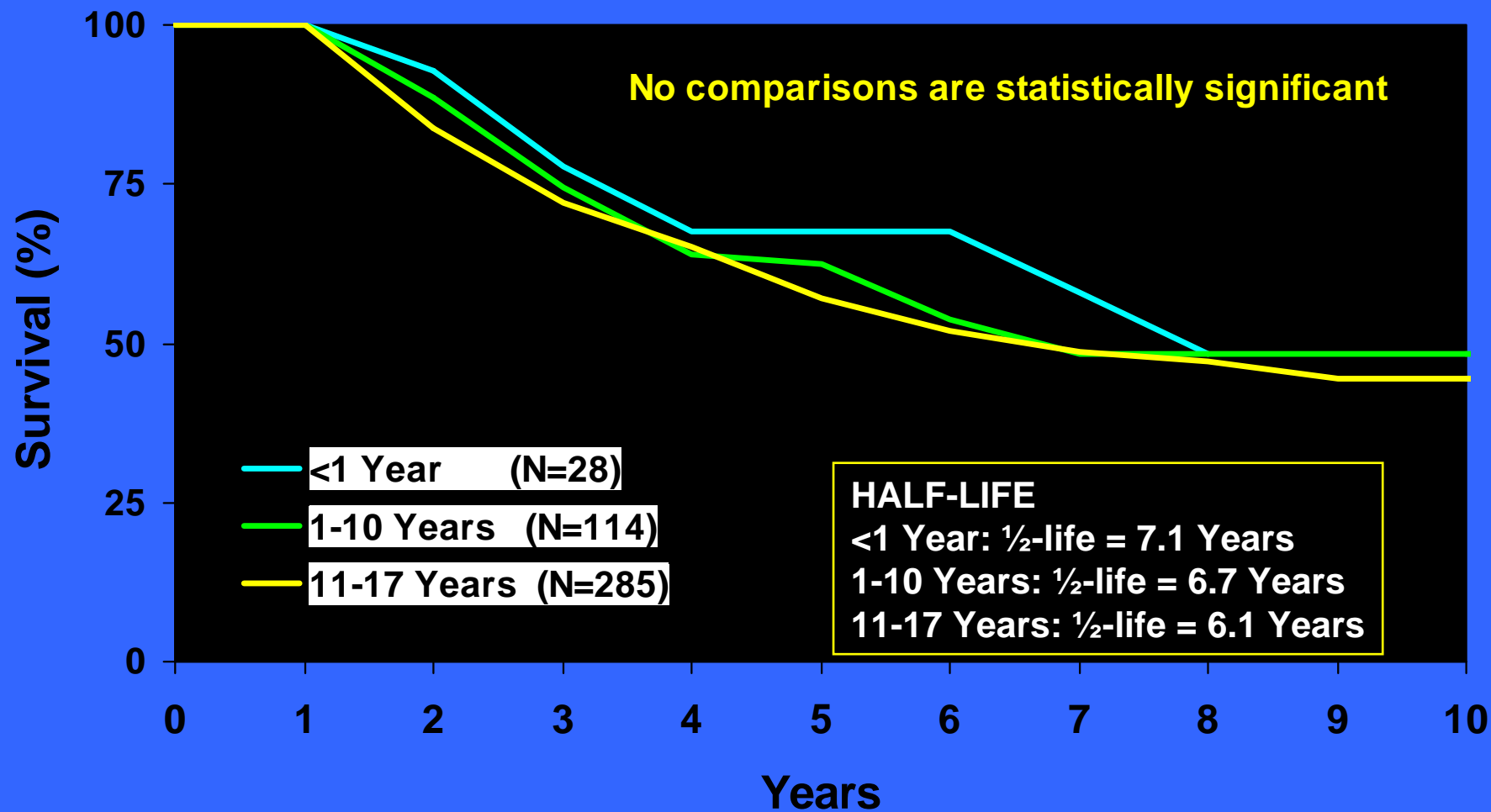
Antiinflammatories
Antiproteases - a1AT

Suppressive
Antibiotics
Organ replacement

PEDIATRIC LUNG TRANSPLANTATION

Conditional Kaplan-Meier Survival by Age Group

(Transplants: January 1990 - June 2002)



Expected mode of action of anti-inflammatory agents in CF

- Early reduction of neutrophil burden & inhibit local proinflammatory (IL-8) cytokines
- Improve lung function
- Reduce number of exacerbations
- Reduce need of hospitalization
- **Affect basal defect ??**

rhDNase as anti-inflammatory principle

- Suri R, et al Am J Respir Crit Care Med. 2002 Aug 1;166(3):352-5
No proinflammatory activity of rhDNase
- Paul K et al Am J Respir Crit Care Med. 2004 Mar 15;169(6):719-25
rhDNase stabilizes inflammatory markers in mild CF in 3-yr study
- Ratjen F et al Thorax. 2002 Nov;57(11):930-4
Metalloproteinase 8 & 9 decrease after 18 mths of treatment